

What is claimed is:

1. A compound having the formula:



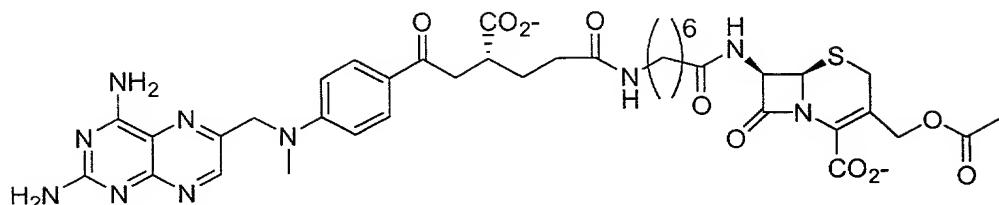
wherein H1 is a substrate capable of selectively binding to a first receptor;

wherein H2 is a substrate capable of selectively binding to and selectively forming a covalent bond with a second receptor; and

wherein Y is a moiety providing a covalent linkage between H1 and H2, which may be present or absent, and when absent, H1 is covalently linked to H2.

2. The compound of claim 1, wherein H1 is a Methotrexate moiety or an analog thereof.
  3. The compound of claim 1, wherein H2 is a cephem moiety capable of selectively binding to and selectively forming a covalent bond with the penicillin-binding-protein ("PBP").
  4. The compound of claim 1, wherein H2 is a fluorouracil moiety capable of selectively binding to and selectively forming a covalent bond with the thymidine synthase ("TS") enzyme.

5. The compound of claim 2 having the structure:



6. A complex between the compound of claim 1 and a fusion protein, the fusion protein comprising a receptor domain which binds to the compound.
  7. The complex of claim 6 wherein the fusion protein further comprises a DNA-binding domain fused to the receptor domain.
  8. The complex of claim 6 wherein the fusion protein further comprises a transcription activation domain fused to the receptor domain.
  9. The complex of claim 6, wherein the receptor domain is dihydrofolate reductase ("DHFR"), penicillin-binding protein ("PBP"), or thymidine synthase ("TS") enzyme.
  10. The complex of claim 9, wherein the PBP is the *Streptomyces* R61 PBP.
  11. The complex of claim 9, wherein the DHFR is the *E.coli* DHFR ("eDHFR").
  12. The complex of claim 7, wherein the fusion protein is eDHFR-LexA or R61-LexA.
  13. The complex of claim 8, wherein the fusion protein is eDHFR-B42 or R61-B42.

14. A cell comprising the complex of claim 6.
15. A cell comprising a DNA sequence which on transcription gives rise to a first fusion protein exogenous to the cell and a second fusion protein exogenous to the cell, wherein the first fusion protein is a receptor domain fused with a DNA-binding domain; and wherein the second fusion protein is a transcription activation domain fused to either a penicillin-binding-protein ("PBP") or to a thymidine synthase ("TS") enzyme.
16. The cell of claim 15, wherein the receptor domain of the first fusion protein is DHFR.
17. The cell of claim 15, wherein the DNA-binding domain of the first fusion protein is LexA.
18. The cell of claim 15, wherein the transcription activation domain of the second fusion protein is B42.
19. The cell of claim 15, wherein the PBP is the *Streptomyces* R61 PBP.
20. The cell of claim 15, wherein the first fusion protein is eDHFR-LexA, and the second fusion protein is R61-B42.
21. The cell of claim 15, where the cell is a yeast cell, a bacteria cell or a mammalian cell.
22. The cell of claim 15, where the cell is *S. cerevisiae* or *E. coli*.

23. A method of dimerizing two fusion proteins inside a cell using the compound of claim 1, comprising the steps of
- providing a cell that expresses a first fusion protein which comprises a receptor domain that binds to H1, and a second fusion protein which comprises a receptor domain that binds to and forms a covalent bond with H2, and
  - contacting the compound with the cell so as to dimerize the two fusion proteins.
24. The method of claim 23, wherein the receptor domain of the first fusion protein is DHFR.
25. The method of claim 23, wherein the DNA-binding domain of the first fusion protein is LexA.
26. The method of claim 23, wherein the transcription activation domain of the second fusion protein is B42.
27. The method of claim 23, wherein the receptor domain of the second fusion protein is a penicillin-binding-protein ("PBP") or to a thymidine synthase ("TS") enzyme.
28. The method of claim 27, wherein the PBP is the *Streptomyces* R61 PBP.
29. The method of claim 23, wherein the first fusion protein is eDHFR-LexA, and the second fusion protein is R61-B42.
30. A method for identifying a molecule that binds a known target in a cell from a pool of candidate molecules, comprising:
- forming a screening molecule by covalently bonding each molecule in the pool of candidate molecules to a substrate capable of selectively binding to and selectively forming a covalent bond with a receptor;

(b) introducing the screening molecule into a cell culture comprising cells that express

a first fusion protein of a DNA-binding domain fused to a known target receptor domain against which the candidate molecule is screened,

a second fusion protein which comprises a receptor domain capable of binding to and forming a covalent bond with the screening molecule, and

a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein, bringing the two fusion proteins in proximity so as to activate the expression of the reporter gene;

(d) selecting the cell that expresses the reporter gene;  
and

(e) identifying the small molecule that binds the known target receptor.

31. The method of claim 30, wherein the cell is selected from the group consisting of insect cells, yeast cells, mammalian cells, and their lysates.

32. The method of claim 30, wherein the DNA-binding domain of the first fusion protein is LexA.

33. The method of claim 30, wherein the transcription activation domain of the second fusion protein is B42.

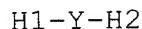
34. The method of claim 30, wherein the receptor domain of the second fusion protein is a penicillin-binding-protein ("PBP") or to a thymidine synthase ("TS") enzyme.

35. The method of claim 34, wherein the PBP is the *Streptomyces* R61 PBP.
36. The method of claim 30, wherein the molecule is obtained from a combinatorial library.
37. The method of claim 30, wherein the steps (b)-(e) of the method are iteratively repeated in the presence of a preparation of random small molecules for competitive binding with the screening molecule so as to identify a molecule capable of competitively binding the known target receptor.
38. A method for identifying an unknown target receptor to which a molecule is capable of binding in a cell, comprising:  
(a) providing a screening molecule having a ligand which has a specificity for the unknown target receptor covalently bonded to a substrate capable of selectively binding to and selectively forming a covalent bond with a receptor;  
(b) introducing the screening molecule into a cell which expresses  
a first fusion protein of a DNA-binding domain fused to the unknown target receptor domain against which the candidate molecule is screened,  
a second fusion protein which comprises a receptor domain capable of binding to and forming a covalent bond with the screening molecule, and  
a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;  
(c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;  
(d) selecting which cell expresses the unknown target receptor; and

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- (e) identifying the unknown target receptor.
39. The method of claim 38, wherein the unknown protein target is encoded by a DNA from the group consisting of genomicDNA, cDNA and syntheticDNA.
40. The method of claim 38, wherein the ligand has a known biological function.

41. A compound having the formula:

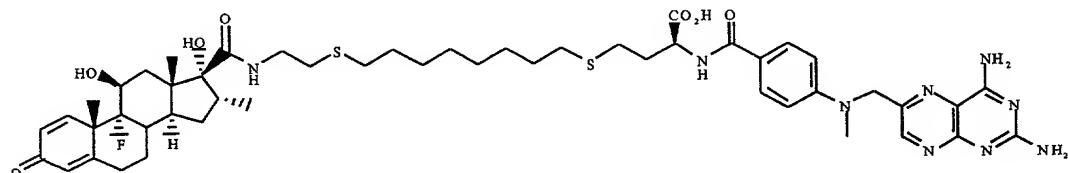


wherein H1 is Mt<sub>x</sub> or an analog thereof;

wherein H2 is a substrate capable of binding to a receptor,  
and

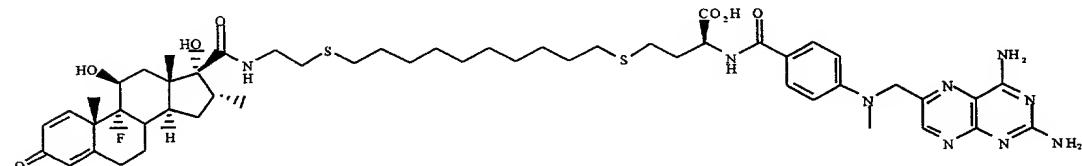
wherein Y is a moiety providing a covalent linkage between  
H1 and H2, which may be present or absent, and when absent, H1  
is covalently linked to H2.

42. The compound of claim 41, having the formula:



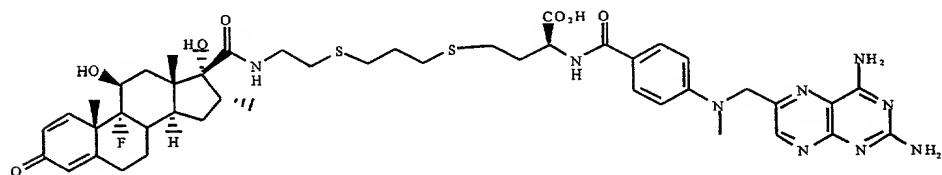
(D8M)

43. The compound of claim 41, having the formula:

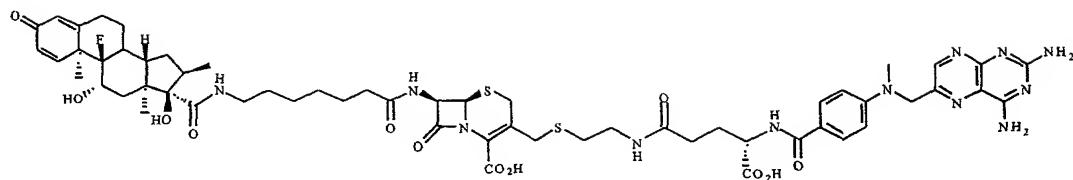


(D10M)

44. The compound of claim 41, having the formula:

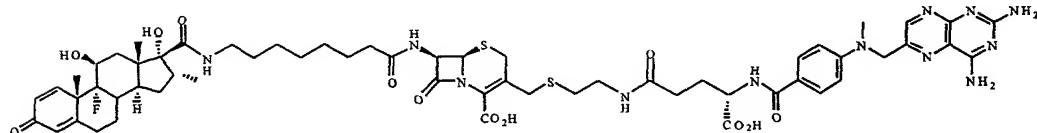


45. The compound of claim 41, having the formula:



(D7CM)

46. The compound of claim 41, having the formula:



(D8CM)

47. A complex between the compound of claim 41 and a fusion protein which comprises a binding domain capable of binding to methotrexate, wherein H1 of the compound binds to the binding domain of the fusion protein.

48. The complex of claim 47, wherein the binding domain is that of the DHFR receptor.

49. The complex of claim 47, wherein the fusion protein is DHFR-LexA.

50. The complex of claim 47, wherein the fusion protein is DHFR-B42.

51. A cell comprising the complex of claim 47.

52. A method for screening a cDNA library by identifying the expressed protein target, comprising:
- (a) providing a screening molecule comprising a methotrexate moiety or an analog of methotrexate covalently bonded to a ligand which has a known specificity;
  - (b) introducing the screening molecule into a cell which expresses a first fusion protein comprising a binding domain capable of binding methotrexate, a second fusion protein comprising the expressed unknown protein target, and a reporter gene wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;
  - (c) permitting the screening molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene;
  - (d) selecting which cell expresses the reporter gene; and
  - (e) identifying the unknown protein target and the corresponding cDNA.
53. The method of claim 52, wherein the unknown protein target is encoded by a DNA from the group consisting of genomicDNA, cDNA and syntheticDNA.
54. A new protein cloned by the method of claim 52.

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